FORM PTO-1390 (Modified) (REV 10-95) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)
06501/024001	09/202464

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/JP97/02031	12 June 1997	14 June 1996

TITLE OF INVENTION

T-CELL EPITOPE PEPTIDES

APPLICANT(S) FOR DO/EO/US

KOHSUKE KINO AND KAZUO DAIRIKI

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ A copy of the International Search Report (PCT/ISA/210).
8. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 13 to 18 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
    A **SECOND** or **SUBSEQUENT** preliminary amendment.
16. ☐ A substitute specification.
17. ☐ A change of power of attorney and/or address letter.
18. ☒ Certificate of Mailing by Express Mail
19. ☐ Other items or information:

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Date of Deposit : DECEMBER 14, 1998

I hereby certify that under 37 CFR 1.10 that this correspondence is being deposited with the United StatesPostal Service as "Express Mail Post Office To Addressee" with sufficient postage on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
	PCT/JP97/02031	06501/024001

20. The following fees are submitted:.	CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :		
☒ Search Report has been prepared by the EPO or JPO **$840.00**		
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) **$670.00**		
☐ No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) **$760.00**		
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2) paid to USPTO **$970.00**		
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) **$96.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	**$840.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	**$0.00**	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	14 - 20 =	0	x $18.00	**$0.00**	
Independent claims	2 - 3 =	0	x $78.00	**$0.00**	
Multiple Dependent Claims **(check if applicable).**			☐	**$0.00**	
	TOTAL OF ABOVE CALCULATIONS =			**$840.00**	
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) **(check if applicable).** ☐				**$0.00**	
	SUBTOTAL =			**$840.00**	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +				**$0.00**	
	TOTAL NATIONAL FEE =			**$840.00**	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☐				**$0.00**	
	TOTAL FEES ENCLOSED =			**$840.00**	
				Amount to be: refunded	$
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☒ A check in the amount of **$840.00** to cover the above fees is enclosed.

☐ Please charge my Deposit Account No. in the amount of to cover the above fees.
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☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **06-1050** A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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SIGNATURE

Janis K. Fraser
NAME

34,819
REGISTRATION NUMBER

December 4, 1998
DATE

PATENT

ATTORNEY DOCKET NO. 06501/024001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Kohsuke Kino et al. Art Unit:
Serial No.: Examiner:
Filed : Herewith
Title : T-CELL EPITOPE PEPTIDES

Int'l Appln. No. : PCT/JP97/02031
Int'l Filing Date: June 12, 1997

Box PCT
Assistant Commissioner for Patents
Washington, DC 20231

PRELIMINARY AMENDMENT

Prior to examination, please amend the application as follows:

In the Claims:

In claim 3, line 1, delete "or 2".

In claim 4, line 4, delete "or 2".

In claim 5, line 3, delete "any one of claims 1 to 4", and insert --claim 1--.

In claim 7, line 3, delete "any one of claims 1 to 4", and insert --claim 1--.

In claim 8, lines 2 and 3, delete "any one of claims 1 to 4", and insert --claim 1--.

In claim 10, lines 2 and 3, delete "any one of claims 1 to 4", and insert --claim 1--.

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Lisa C. Gray
Lisa C. Gray

Cancel claims 6 and 9.

Add new claims 11 through 16.

-- 11. The peptide of claim 2, wherein said peptide comprises at least two T-cell epitopes.

12. A peptide having an effect to stimulate and/or suppress activities of T-cells derived from patients with pollinosis caused by tree pollens in springtime and having the amino acid sequence as described in claim 2 which is modified by substitution, deletion, or insertion.

13. A composition for peptide-based immunotherapy of pollinosis caused by tree pollens in springtime, comprising the peptide of claim 2 as an effective ingredient.

14. A method for treating or preventing pollinosis caused by tree pollens in springtime, comprising administering the peptide of claim 2.

15. A reagent for diagnosing pollinosis caused by tree pollens in springtime, comprising the peptide of claim 2 as an effective ingredient.

16. A method for diagnosing pollinosis caused by tree pollens in springtime, comprising administering the peptide of claim 2. --

REMARKS

Claims 1-5, 7, 8, and 10-16 are pending in the application, claims 6 and 9 having been cancelled and new claims 11-16 added by the above amendment. Claims 3-5, 7, 8, and 10 are amended to remove multiple dependencies. New claims 11-16 are derived from original claims 3-5, 7, 8, and 10, respectively.

No new matter has been added.

Please apply any charges not covered, or any credits, to Deposit Account No. 06-1050.

Respectfully submitted,

Date: Dec. 14, 1998

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T-CELL EPITOPE PEPTIDES

Technical Field

The present invention relates to T-cell epitope peptides of pollen allergen and a composition for peptide-based immunotherapy comprising the peptides as an effective ingredient. This composition is useful for treating and/or preventing pollinosis in springtime.

Background Art

About 10% of the Japanese population suffers from pollinosis developed in springtime such as cedar pollinosis. This condition has been on the increase and is attracting public attention.

The period when pollinosis is developed generally corresponds to the period when pollens scatter. In many cases, symptoms of pollinosis still remain after the season in which cedar pollens scatter because most patients with cedar pollinosis are also sensitized with Japanese cypress pollens (Hiroki cypress pollens) that start to scatter just after the cedar pollen-scattering period. Thus, patients who are also sensitive to Japanese cypress pollens suffer from the symptoms of pollinosis for a significant portion of the year.

Cedar pollens and Japanese cypress pollens possess common antigenicity (Takeshi Ide et al., Allergy Clinic 11, 174-178, 1991). The cross-reactivity of IgE antibodies between cedar pollens and Japanese cypress pollens has been established (Taniai M. et al., Mol. Immunol. 30, 183-189, 1993). The

positivity index of patients with spring pollinosis for their allergen-specific IgE antibodies is 83.5% for cedar pollens, 80.0% for Japanese cypress pollens, and 76.4% for both pollens (Mitsuhiro Okano et al., Allergy 43, 1179-1184, 1994). In addition, 60% of the patients with cedar pollinosis possess Japanese cypress pollen-specific IgE antibodies (Yozo Saito, Chiryo (Therapy) 78, 1571-1576, 1996). Based on these reports, it is generally recognized that cedar pollinosis patients can develop pollinosis to Japanese cypress pollens and vice versa.

Pollinosis is a typical immediate type I allergy induced by an antigen-antibody reaction between a pollen allergen (which is an antigen causing allergy and is substantially the same as an antigen) and an IgE antibody specific to the allergen. Thus, pollinosis is now prevented and treated using methods theoretically based on the mechanism by which type I allergics develop. This mechanism is briefly described below.

An antigen that has invaded the body is presented to helper T cells by antigen-presenting cells. As a result, B cells mature into antibody-producing cells. The antibody-producing cells produce an antigen-specific IgE antibody, which binds to the surface of mast cells. A subsequently invaded antigen binds to the IgE antibody on the mast cells. This stimulation releases chemical mediators like histamine from the mast cells, thereby causing an allergic symptom.

The following three methods are mainly used to prevent and treat allergies based on the above mechanism: 1) evasion of an antigen that causes allergy, 2) chemotherapy typically

using an anti-histaminic, and 3) desensitization therapy using an allergen. However, method 1) is difficult to implement practically, and method 2) is merely symptomatic therapy. Method 3) is expected to be the only treatment attacking the root problem, but it is not always effective and may possibly cause serious side effects such as anaphylactic shock.

For these reasons, peptide-based immunotherapy using T-cell epitope peptides of allergen has been recently attempted to prevent and treat allergies. T-cell epitopes participate in initiating and retaining an immune response to a protein allergen that causes clinical symptoms of allergies. These T-cell epitopes bind to HLA class II molecules on the surface of antigen-presenting cells to stimulate the related T-cell subpopulation. The stimulation is thought to trigger an initial response at the helper T-cell level. This initial response causes proliferation of T cells, secretion of lymphokines, a localized inflammatory response, migration of proliferated immune cells to the inflammatory sites, and activation of the B-cell cascade that precedes antibody production. IgE antibodies that are isotypes of these antibodies are critical to the development and retention of allergies. Furthermore, their production is influenced by the properties of lymphokines secreted by helper T cells at the beginning of the above-described cascade. The T-cell epitope is a basic element or the minimum unit to be recognized by a T-cell receptor. This epitope contains amino acid sequence necessary to recognize the receptor. Allergic inflammation

can be treated by controlling the response of the helper T cell, which plays a key role in immunosuppression, using the T-cell epitope peptide.

Known therapeutic agents for allergies using T-cell epitope peptides include a therapeutic composition comprising a T-cell epitope peptide of cat-origin allergen (a PCT application published in Japan (JP-WA) No. Hei 7-505365), a therapeutic composition comprising a T-cell epitope peptide of cedar pollen Cry j 1 (JP-WA-Hei 8-502163), and a multi-epitope peptide obtained by joining T-cell epitopes of cedar pollens Cry j 1 and Cry j 2 (Japanese Patent Application No. Hei 8-80702). The main allergen of Japanese cypress pollen, Cha o 1, is reported to have molecular weights of 45 KD or 50 KD. Each molecule has the same isoelectric point of 6.8 and consists of a protein containing 5% carbohydrate (Takeshi Ide, et al., Nippon Kafun Gakkaishi (Journal of the Japanese Pollen Association) 34, 39, 1988). However, their primary structures are unknown, and accordingly, no T-cell epitope site has been identified on the allergen molecules yet. Recently, the present inventors succeeded in cloning the Japanese cypress pollen allergen gene, and clarified that, in addition to Cha o 1, another type of the allergen, Cha o 2, was present. Furthermore, the primary structures of Cha o 1 and Cha o 2 were determined (Japanese Patent Application No. Hei 6-335089).

Disclosure of the Invention

The period when cedar pollen scatter overlaps that of Japanese cypress pollen is referred to as the mixed

pollen-scattering period. These two pollens possess a common antigenicity, which makes it difficult to distinguish symptoms caused by cedar pollens from those caused by Japanese cypress pollens. The symptoms sometimes continue or develop even after the cedar pollen-scattering period. Since pollens found in the air during that period are mostly Japanese cypress pollens, these symptoms seem to be caused by Japanese cypress pollens. Since more Japanese cypress trees are planted than cedar trees, the amount of scattered Japanese cypress pollen is increasing year after year and will exceed that of cedar pollens in the near future. It is thus desirable to establish a method for preventing and treating allergies based on the root overall pollinosis caused by tree pollens in springtime, including Japanese cypress pollinosis and cedar pollinosis. Peptide-based immunotherapy using T-cell epitope peptides is expected to lead to allergy treatment based on the root pollinosis. As described above, several methods for such immunotherapy are known for cedar pollinosis. However, nothing has been reported on Japanese cypress pollinosis or on pollinosis caused by tree pollens in springtime, including cedar and Japanese cypress pollens.

An objective of the present invention is to provide T-cell epitope peptides useful for peptide-based immunotherapy for Japanese cypress pollinosis. Another objective of the present invention is to provide T-cell epitope peptides useful for peptide-based immunotherapy for patients with pollinosis caused by tree pollens in springtime including patients with

cedar pollinosis who show a cross-reactivity with Japanese cypress pollens.

The present inventors have identified a T-cell epitope site on the allergen molecules of Japanese cypress pollen by stimulating a T-cell line established from patients with Japanese cypress pollinosis with synthetic overlapping peptides that cover the entire primary structure of Japanese cypress pollen allergens, thus solving the above problems.

The present invention is comprised of the inventions described in each claim and will be described below in more detail.

The present inventors determined the amino acid sequence (described in Japanese Patent Application No. Hei 6-335089) of the major allergen, Cha o 1 (mature protein), of Japanese cypress pollen allergen shown as SEQ ID NO: 1 and that of Cha o 2 shown as SEQ ID NO: 2. The amino acid sequence of Cha o 1 has 80% homology to cedar pollen allergen Cry j 1, and that of Cha o 2 has 75% homology to cedar pollen allergen Cry j 2.

A number of amino acid substitutions are observed in the allergens derived from pollens, mites, and bee venom. These allergen species are called isoallergens. For example, eleven isoallergens have been isolated from birch tree pollen Bet v I, and their amino acid sequences differ from each other within a range of 2 to 15% (Swoboda, I. et al., J. Biol. Chem. 270: 2607-2613, 1995). At present, two isoallergens, in which six amino acid residues are substituted in a mature protein region, have been found in Cry j 2 (unexamined published Japanese Patent

Applications (JP-A) No. Hei 8-47392 and No. Hei 7-170986). One skilled in the art can reasonably expect that isoallergens would be present in Cha o 1 and Cha o 2 as well. Such isoallergens are also included in Cha o 1 and Cha o 2 referred to in the present invention.

The family of cedar trees is classified into nine genera, and the family of Japanese cypress, into seven genera. It is reported that allergens from Cryptomeria, Redwood, and Metasequoia, which belong to the cedar (Taxodiaceae) family, and Umbrella Pine, which is hypothesized to belong to either an independent family, the cedar family, or the pine family, show reactivity with those from Japanese Cypress, Sawara Cypress, Oriental Arbor-vitae, Needle Juniper、and Chinese Juniper, which belong to the family of Cupressaceae (Takeshi Ide, et al., Allergy Clinic, 11, 174-178, 1991). In view of this report, cedar allergens are broadly cross-reactive with the allergens of Japanese cypress. Therefore, the peptides of the present invention are generally effective not only for Japanese cypress pollinosis but also for cedar pollinosis as well.

To obtain the T-cell epitope peptides of the present invention, overlapping peptides that cover the entire primary structures of Cha o 1 and Cha o 2 were synthesized; each peptide consists of the adequate number of amino acid residues (12 to 20 residues). The peptide of the present invention stimulates and/or suppresses the activity of T cells derived from patients with pollinosis caused by tree pollens in springtime. In other

words, the peptide of the present invention can induce proliferation of T cells or responses of T cells such as secretion of lymphokines, and/or can induce T-cell anergy (non-responsive). T-cell epitope sites on the allergen molecules can be identified using T-cell growth as an index in accordance with the method described in JP-A-Hei 8-47392. In particular, T-cell lines or T-cell clones, which are specifically reactive with Cha o 1 and Cha o 2, are established for every patient from peripheral lymphocytes of a patient with Japanese cypress pollinosis. The T-cell lines or T-cell clones are cultured in the presence of each peptide of the overlapping peptides. The epitope sites are identified by measuring the proliferation of T cells in the presence of the peptide (e.g., uptake of [^{3}H]thymidine into the cells) and calculating a stimulation index. The stimulation index (SI) used herein is obtained by dividing the radioactive level of [^{3}H]thymidine (cpm) taken up into the cells in the presence of the peptide by the level of [^{3}H]thymidine (cpm) taken up into the cells in the absence of the peptide (control). Based on the thus-obtained data, a mean stimulation index for each peptide is calculated for each patient group. The peptides found to induce T-cell response and/or induce T-cell anergy are defined as having a T-cell stimulating activity. The preferable T-cell epitope peptides of the present invention possess a T-cell stimulating activity and thus contain at least one T-cell epitope. Examples of the T-cell epitope peptide of Cha o 1 shown in Fig. 1 (specifically shown in Fig. 2, Fig. 3, and SEQ ID

NO: 3 through SEQ ID NO: 37) include Peptide #1-2 (SEQ ID NO: 4), Peptide #1-4 (SEQ ID NO: 6), Peptide #1-5 (SEQ ID NO: 7), Peptide #1-6 (SEQ ID NO: 8), Peptide #1-7 (SEQ ID NO: 9), Peptide #1-8 (SEQ ID NO: 10), Peptide #1-10 (SEQ ID NO: 12), Peptide #1-11 (SEQ ID NO: 13), Peptide #1-12 (SEQ ID NO: 14), Peptide #1-14 (SEQ ID NO: 16), Peptide #1-15 (SEQ ID NO: 17), Peptide #1-16 (SEQ ID NO: 18), Peptide #1-19 (SEQ ID NO: 21), Peptide #1-20 (SEQ ID NO: 22), Peptide #1-21 (SEQ ID NO: 23), Peptide #1-22 (SEQ ID NO: 24), Peptide #1-23 (SEQ ID NO: 25), Peptide #1-24 (SEQ ID NO: 26), Peptide #1-25 (SEQ ID NO: 27), Peptide #1-26 (SEQ ID NO: 28), Peptide #1-27 (SEQ ID NO: 29), Peptide #1-30 (SEQ ID NO: 32), Peptide #1-31 (SEQ ID NO: 33), Peptide #1-32 (SEQ ID NO: 34), Peptide #1-33 (SEQ ID NO: 35), and Peptide #1-34 (SEQ ID NO: 36) (Fig. 4). Examples of the T-cell epitope peptide of Cha o 2 shown in Fig. 5 (specifically shown in Fig. 6, Fig. 7, and SEQ ID NO: 38 through SEQ ID NO: 88) include Peptide #2-5 (SEQ ID NO: 42), Peptide #2-7 (SEQ ID NO: 44), Peptide #2-8 (SEQ ID NO: 45), Peptide #2-9 (SEQ ID NO: 46), Peptide #2-10 (SEQ ID NO: 47), Peptide #2-11 (SEQ ID NO: 48), Peptide #2-12 (SEQ ID NO: 49), Peptide #2-13 (SEQ ID NO: 50), Peptide #2-14 (SEQ ID NO: 51), Peptide #2-15 (SEQ ID NO: 52), Peptide #2-16 (SEQ ID NO: 53), Peptide #2-17 (SEQ ID NO: 54), Peptide #2-18 (SEQ ID NO: 55), Peptide #2-19 (SEQ ID NO: 56), Peptide #2-20 (SEQ ID NO: 57), Peptide #2-21 (SEQ ID NO: 58), Peptide #2-22 (SEQ ID NO: 59), Peptide #2-23 (SEQ ID NO: 60), Peptide #2-24 (SEQ ID NO: 61), Peptide #2-25 (SEQ ID NO: 62), Peptide #2-26 (SEQ ID NO: 63), Peptide #2-27 (SEQ ID NO: 64),

Peptide #2-30 (SEQ ID NO: 67), Peptide #2-31 (SEQ ID NO: 68), Peptide #2-32 (SEQ ID NO: 69), Peptide #2-33 (SEQ ID NO: 70), Peptide #2-34 (SEQ ID NO: 71), Peptide #2-35 (SEQ ID NO: 72), Peptide #2-36 (SEQ ID NO: 73), Peptide #2-37 (SEQ ID NO: 74), Peptide #2-38 (SEQ ID NO: 75), Peptide #2-40 (SEQ ID NO: 77), Peptide #2-41 (SEQ ID NO: 78), Peptide #2-42 (SEQ ID NO: 79), and Peptide #2-43 (SEQ ID NO: 80) (Fig. 8). More preferably, the T-cell epitope peptides have a mean stimulation index of 2.0 or more. Examples include Peptide #1-2 (SEQ ID NO: 4), Peptide #1-7 (SEQ ID NO: 9), Peptide #1-8 (SEQ ID NO: 10), Peptide #1-20 (SEQ ID NO: 22), Peptide #1-22 (SEQ ID NO: 24), Peptide #1-24 (SEQ ID NO: 26), Peptide #1-26 (SEQ ID NO: 28), Peptide #1-32 (SEQ ID NO: 34), Peptide #1-33 (SEQ ID NO: 35), and Peptide #1-34 (SEQ ID NO: 36), which are shown in Fig. 1, and Peptide #2-10 (SEQ ID NO: 47), Peptide #2-20 (SEQ ID NO: 57), Peptide #2-21 (SEQ ID NO: 58), Peptide #2-40 (SEQ ID NO: 77), Peptide #2-41 (SEQ ID NO: 78), Peptide #2-42 (SEQ ID NO: 79), and Peptide #2-43 (SEQ ID NO: 80), which are shown in Fig. 5. Most preferably, the T-cell epitope peptide has a minimum positivity index of 100. Examples thereof include Peptide #1-7 (SEQ ID NO: 9), Peptide #1-22 (SEQ ID NO: 24), Peptide #1-32 (SEQ ID NO: 34), and Peptide #1-33 (SEQ ID NO: 35), which are shown in Fig. 1, and Peptide #2-10 (SEQ ID NO: 47), Peptide #2-20 (SEQ ID NO: 57), Peptide #2-40 (SEQ ID NO: 77), Peptide #2-41 (SEQ ID NO: 78), Peptide #2-42 (SEQ ID NO: 79), and Peptide #2-43 (SEQ ID NO: 80), which are shown in Fig. 5. The "positivity index" used herein is obtained by multiplying a

mean stimulation index of a peptide by appearance frequency (%) of patients showing a T-cell response to the peptide.

To identify the epitope accurately, a peptide having the T-cell stimulating activity and thus containing at least one T-cell epitope may be modified by deleting any of the amino acid residues at the amino terminus or the carboxyl terminus of the peptide. The modified peptide may then be examined for any change in the T-cell stimulating activity. When two or more peptides that share the overlapping region exhibit the T-cell stimulating activity, a new T-cell epitope peptide containing all or part of the overlapping peptides is prepared, and its T-cell stimulating activity is measured in the same manner.

The T-cell epitope peptide of the present invention may possibly be immunologically associated with Cry j 1 or Cry j 2 in the T-cell cross-reactivity. Specifically, 1) the amino acid sequence of Cha o 1 has 80% homology to that of Cry j 1, and the amino acid sequence of Cha o 2 has 75% homology to that of Cry j 2; 2) the amino acid sequence of T-cell epitope peptide #1-2 of Cha o 1 (corresponding to the amino acid sequence, SEQ ID NOS: 11-30, of mature type Cha o 1), which was identified in Example 5 of the present invention, is identical with the amino acid sequence of T-cell epitope peptide CJI-1 of Cry j 1 (corresponding to the amino acid sequence, SEQ ID NOS: 11-30, of mature type Cry j 1; see Fig. 13 of JP-A-Hei 8-502163) except for two amino acid residues (Ala at position 12 of Cha o 1 corresponds to Ser of CJI-1, and Asp at position 15 of Cha o 1 corresponds to Ala of CJI-1); and 3) both cedar pollens and

Japanese cypress pollens have a common antigenicity. For these reasons, the origin of the T-cell epitope of the present invention is not limited to Japanese cypress. The T-cell epitope peptide of the present invention is effective not only for Japanese cypress pollinosis but also for cedar pollinosis.

In the T-cell epitope peptide of the present invention, the amino acid residues that participate in recognizing the T-cell receptor can be determined by a known method (for example, measuring the change in the T-cell stimulating activity which might occur due to the substitution of amino acid residues). The amino acid residues found to be essential for an interaction with the T-cell receptor are substituted with other amino acid residues to antigen-specifically control the T-cell stimulating activity so that allergic inflammation can be suppressed (increase the reactivity of T cells, alter the lymphokine-producing pattern, anergy etc.). It has been reported that, when one amino acid residue at the T-cell recognition site of the T-cell epitope peptide of cedar pollen Cry j 1 was substituted with another amino acid residue (substituting Thr at position 399 with Val) in a human allergy model, the resulting analog peptide showed substantially the same T-cell growth and IL-4 production as those of a wild type peptide, but showed increased production of IFN-γ that suppressed the production of IgE antibodies (Ikagawa, S. et al., J. Aller. Clin. Immunol. 97, 54-64, 1996). It has further been revealed that a binding motif of HLA class II molecules consists of three to five amino acid residues arranged via one

or two intermediary amino acid residues. When these residues consist of several kinds of specified amino acids, the peptide binds to the HLA class II molecules (Matsushita, S. et al., J. Exp. Med. 180: 877-883, 1994). Therefore, allergic inflammation can be prevented by determining the amino acid residues of the T-cell epitope peptide of the present invention, which are essential for the interaction with HLA class II molecules, by a known method, and substituting the thus-determined amino acid residues with other amino acid residues. Furthermore, the T-cell epitope peptide of the present invention can be modified so as to improve its solubility, thereby increasing its therapeutic or preventing effects or stability. Such modification includes substitution, deletion, and addition of the amino acid residues.

In the present invention, the T-cell epitope peptide preferably does not bind to IgE antibodies. Even if it binds to the IgE antibodies, the degree of binding is substantially lower than that of binding of the allergen of natural Japanese cypress pollens, from which the peptide is derived, to the antibodies.

The T-cell epitope peptide of the present invention preferably contains at least seven amino acid residues. These regions may be joined via a linker such as Arg-Arg or Lys-Lys that is sensitive to cleavage with an enzyme such as cathepsin or trypsin to enhance the sensitivity to processing by antigen-presenting cells. Thus, a peptide region can be produced to contain one or more T-cell epitopes. The T-cell

epitope peptide of the present invention may be used in combination with other peptides such as a T-cell epitope peptide of Cry j 1 (JP-WA-Hei 8-502163) and/or a T-cell epitope peptide of Cry j 2 (JP-WA-Hei 8-47392).

When a peptide containing at least one T-cell epitope peptide of the present invention is administered to an individual sensitive to Japanese cypress pollens and/or an individual sensitive to both Japanese cypress and cedar pollens, the peptide can control the individual's allergic response to the allergen(s). Such a peptide is thus effective for peptide-based immunotherapy. In particular, the T-cell epitope peptide of the present invention in combination with the T-cell epitope peptide of cedar pollen is more effective for peptide-based immunotherapy for a patient with pollinosis caused by tree pollens in springtime, represented by cedar and Japanese cypress pollens.

The T-cell epitope peptide of the present invention may be used as a diagnostic tool for pollinosis caused by Japanese cypress pollen allergens or other tree pollens that are immunologically cross-reactive with Japanese cypress pollen allergens. In such an application, the T-cell epitope peptide of the present invention is added to peripheral lymphocytes collected from a patient in an amount of about 0.1 μg/ml to about 1 mg/ml, and preferably about 1 to about 300 μg/ml. After the mixture is incubated for a week, uptake of [^{3}H]thymidine into the lymphocytes is assayed and assessed for diagnosis of pollinosis. The T-cell epitope peptide of the present

invention may also be used to evaluate either the function of T cells or proliferation of T cells or both of them.

When the T-cell epitope peptide of the present invention is synthesized using recombinant DNA technology, host cells transformed with a nucleic acid containing a sequence coding for the peptide are cultured in a medium suitable for growing the host cells. The peptide can be harvested from the culture supernatant or from the host cells by a method known in the art. E. coli, yeasts, or mammal cells can be used as such host cells.

When the T-cell epitope peptide of the present invention is used in peptide-based immunotherapy for patients with pollinosis, the peptide may be administered together with pharmaceutically acceptable diluents or carriers. The "patient with pollinosis" as used herein includes patients with cedar pollinosis who show immunological cross-reactivity with the allergen of Japanese cypress pollen. The T-cell epitope peptide of the present invention can be administered in a simple manner, for example, by injection (subcutaneous or intravenous), instillation, rhinenchysis, oral administration, inhalation, or percutaneous administration. In the case of injection, a single dose of the peptide ranges preferably from about 1μg to about 30 mg, and more preferably from about 20 μg to about 10 mg.

Brief Description of the Drawings

Figure 1 shows T-cell epitope peptides of the Japanese cypress pollen allergen, Cha o 1, and a positivity index of

each peptide.

Figure 2 shows overlapping peptides (#1-1 to #1-28) of Cha o 1.

Figure 3 shows overlapping peptides (#1-29 to #1-35) of Cha o 1.

Figure 4 shows peptides containing T-cell epitopes of Cha o 1.

Figure 5 shows T-cell epitope peptides of Japanese cypress pollen allergen, Cha o 2, and a positivity index of each peptide.

Figure 6 shows overlapping peptides (#2-1 to #2-27) of Cha o 2.

Figure 7 shows overlapping peptides (#2-28 to #2-51) of Cha o 2.

Figure 8 shows peptides containing T-cell epitopes of Cha o 2.

Best Mode for Implementing the Invention

Examples of the present invention will be described below, but are not to be construed to limit the scope of the present invention.

Example 1

Synthesis of overlapping peptides

Based on the amino acid sequences of Japanese cypress pollen allergens Cha o 1 (SEQ ID NO: 1) and Cha o 2 (SEQ ID NO: 2), overlapping peptides consisting of 20 amino acid residues (14 residues in Peptide #1-35 (SEQ ID NO: 37) and Peptide #2-51 (SEQ ID NO: 88), each containing 10 overlapping

residues) were synthesized by the Fmoc method using a peptide synthesizer (PSSM-8, Shimadzu Seisakusho Ltd.). Thirty-five kinds of overlapping peptides were prepared for Cha o 1 (Fig. 1, SEQ ID NO: 3 through SEQ ID NO: 37), and 51 kinds, for Cha o 2 (Fig. 5, SEQ ID NO: 38 through SEQ ID NO: 88). The thus-synthesized peptides were all purified by high-performance liquid chromatography (HPLC) using an ODS column. The purity was 90% or higher in all of the peptides. The molecular weights of the purified peptides were identified by using a LASERMAT 2000 (Finnigan MAT Ltd.).

Example 2

Expression of the recombinant proteins in E. coli

Using a PCR technique, cDNA was amplified from plasmid DNA, in which Cha o 1 cDNA or Cha o 2 cDNA encoding a Japanese cypress pollen antigen had been cloned (Japanese Patent Application No. Hei 6-335089). A restriction enzyme recognition site was attached to the terminus of each cDNA. This DNA fragment was inserted into a histidine-tagged protein expression vector, pQE9, and the resulting vector was used to transform E. coli M15 (pREP4). Expression of the gene transformed was confirmed for ampicillin-resistant clones by SDS-polyacrylamide gel electrophoresis. The protein expressed was purified using a Ni-NTA agarose affinity column.

Example 3

Establishment of T-cell line

A T-cell line on Cha o 1 was established as follows. Peripheral lymphocytes collected from 19 patients found

positive to Japanese cypress pollinosis using Ala STAT (Nippon DPC Corporation) or CAP-RAST (Pharmacia) were separated by specific gravity centrifugation using Ficoll-Paque. The lymphocytes (2×10^6 cells) were suspended in RPMI 1640 medium (GIBCO, Inc.) supplemented with 2 ml of plasma from the same patient (10%) or human AB type serum (20%, Banpoh Tsusho Co., Ltd.). The suspension was incubated on a 24-well plate for 3 to 10 days (37℃, CO_2 incubator, TABAI, Inc.), together with 10 to 30μg/ml of the recombinant Cha o 1 obtained in Example 2 or with a mixture of the overlapping peptides (0.01 to 1 μM) obtained in Example 1. When T cells activated by Cha o 1 stimulation were verified microscopically, 5 U/ml of IL-2 (Boehringer Mannheim) was added to the system, followed by incubation overnight. On the next day, the medium was replaced with fresh RPMI 1640 medium supplemented with 20 U/ml of IL-2, 10% or 20% human AB type serum. Incubation was continued for about 10 days with the medium being replaced every day in the same manner. The T-cell line proliferated was examined for its specificity, and a part of the T-cell line was frozen and stored. A T-cell line stimulated by Cha o 2 was also established from 20 patients with Japanese cypress pollinosis in the same way.

Example 4

Establishment of antigen-presenting cells

A lymphoblastoid cell line (B cell line) transformed by infecting EB virus (Epstein-Barr virus, EBV) to B lymphocytes was established to serve as antigen-presenting cells. First, EBV-producing B-95-8 cells (marmoset, ATCC CRL 1612) were

cultured in RPMI 1640 medium supplemented with 20% inactivated fetal calf serum (FCS, GIBCO Inc.). The culture supernatant was filtered through a 0.22μm sterile filter. The filtrate was frozen and stored at -80℃. Next, 1 ml of EBV solution was added to lymphocytes (2 x 10^6 cells) of a patient with Japanese cypress pollinosis, and the mixture was maintained at 37℃ for 30 minutes for infection. The EBV-infected cells were washed twice then incubated for about 20 days in 20% FCS-RPMI 1640 medium supplemented with a final concentration of 200 ng/ml of Cyclosporin (Sandoz Pharmaceutical Co., Ltd.). After the cell mass was observable by the naked eye, incubation was continued in 20% FCS-RPMI 1640 medium for another 20 days. The resulting cells were frozen and stored until they were used.

Example 5

Identification of T-cell epitope peptide

The cultured B cell line established in Example 4 was treated with 50μg/ml of mitomycin C (Sandoz Pharmaceutical Co., Ltd.) for 30 minutes or exposed to an X ray (50 g ray), followed by washing four times with RPMI 1640 medium. After the B cells were inoculated on a 96-well plate (10,000 cells/well), the recombinant Cha o 1 or Cha o 2 was added thereto in a final concentration of 10 g/ml. To the control group was added a hemolytic streptococcus cell wall antigen (SCW) in a final concentration of 10μg/ml, Candida albicans antigen (CA) in a final concentration of 10μg/ml, and a Tuberculin antigen (PPD) in a final concentration of 1μg/ml). Subsequently, the T-cell line (20,000 cells/well) from the same patient, whose B

cell line had been established, was inoculated into each well. After 48-hour incubation, 0.5μCi [3H]thymidine was added to each well, and incubation was continued for a further 16 hours. After the cells were collected on a glass filter using a cell harvester (Berthold), an uptake of [3H]thymidine into the cells was measured with a liquid scintillation counter to confirm the cell growth response.

After the T-cell line was confirmed to have proliferated specifically in response to Cha o 1 or Cha o 2, the growth response of the T-cell line to each of the overlapping peptides (final concentration of 1 μM) was examined in the same manner as above using the T-cell line established in Example 3. A mean stimulation index of the T-cell line in growth response to the overlapping peptides, an appearance frequency, and a positivity index calculated therefrom are shown in Figs. 1 and 5.

In addition, growth response of the T-cell line (N = 17) to modified sequences (SEQ ID NO: 89 and NO: 90) that corresponded to the amino acid sequences #2-11 and #2-12 in which one amino acid residue had been substituted, was examined. These two modified sequences exhibited T-cell stimulating activity of 1.6 and 1.2 in terms of the stimulation index, 16% and 11% in terms of the appearance frequency, and 25.6 and 13.2 in terms of the positivity index. As demonstrated above, the T-cell epitope peptide of the present invention retained its T-cell stimulating activity even when one or more amino acid residues were mutated, and the activity was enhanced in some

cases.

Industrial Applicability

The present invention provides peptides containing at least one T-cell epitope of Cha o 1 or Cha o 2, which are major allergens of Japanese cypress pollens. The present invention further includes a peptide fragment of other tree pollens showing immunological T-cell cross-reactivity with the peptides. These peptides are effective for peptide-based immunotherapy of pollinosis caused by tree pollens in springtime as represented by cedar and Japanese cypress pollens.

Sequence Listing

SEQ ID NO: 1:
SEQUENCE LENGTH: 354
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: protein
SEQUENCE DESCRIPTION:

```
Asp Asn Pro Ile Asp Ser Cys Trp Arg Gly Asp Ala Asn Trp Asp Gln
                5                  10                  15
Asn Arg Met Lys Leu Ala Asp Cys Ala Val Gly Phe Gly Ser Ser Ala
            20                  25                  30
Met Gly Gly Lys Gly Gly Ala Phe Tyr Thr Val Thr Ser Ser Asp Asp
        35                  40                  45
Asp Pro Val Asn Pro Ala Pro Gly Thr Leu Arg Tyr Gly Ala Thr Arg
    50                  55                  60
Glu Arg Ser Leu Trp Ile Ile Phe Ser Lys Asn Leu Asn Ile Lys Leu
65                  70                  75                  80
Asn Met Pro Leu Tyr Ile Ala Gly Asn Lys Thr Ile Asp Gly Arg Gly
                85                  90                  95
Ala Glu Val His Ile Gly Asn Gly Gly Pro Cys Leu Phe Met Arg Thr
            100                 105                 110
Val Ser His Val Ile Leu His Gly Leu Asn Ile His Gly Cys Asn Thr
        115                 120                 125
Ser Val Ser Gly Asn Val Leu Ile Ser Glu Ala Ser Gly Val Val Pro
    130                 135                 140
Val His Ala Gln Asp Gly Asp Ala Ile Thr Met Arg Asn Val Thr Asp
145                 150                 155                 160
Val Trp Ile Asp His Asn Ser Leu Ser Asp Ser Ser Asp Gly Leu Val
                165                 170                 175
Asp Val Thr Leu Ala Ser Thr Gly Val Thr Ile Ser Asn Asn His Phe
            180                 185                 190
Phe Asn His His Lys Val Met Leu Leu Gly His Ser Asp Ile Tyr Ser
        195                 200                 205
Asp Asp Lys Ser Met Lys Val Thr Val Ala Phe Asn Gln Phe Gly Pro
    210                 215                 220
```

Asn Ala Gly Gln Arg Met Pro Arg Ala Arg Tyr Gly Leu Ile His Val
225 230 235 240
Ala Asn Asn Asn Tyr Asp Pro Trp Ser Ile Tyr Ala Ile Gly Gly Ser
245 250 255
Ser Asn Pro Thr Ile Leu Ser Glu Gly Asn Ser Phe Thr Ala Pro Asn
260 265 270
Asp Ser Asp Lys Lys Glu Val Thr Arg Arg Val Gly Cys Glu Ser Pro
275 280 285
Ser Thr Cys Ala Asn Trp Val Trp Arg Ser Thr Gln Asp Ser Phe Asn
290 295 300
Asn Gly Ala Tyr Phe Val Ser Ser Gly Lys Asn Glu Gly Thr Asn Ile
305 310 315 320
Tyr Asn Asn Asn Glu Ala Phe Lys Val Glu Asn Gly Ser Ala Ala Pro
325 330 335
Gln Leu Thr Lys Asn Ala Gly Val Leu Thr Cys Ile Leu Ser Lys Pro
340 345 350
Cys Ser

SEQ ID NO: 2:
SEQUENCE LENGTH: 514
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: protein
SEQUENCE DESCRIPTION:
Met Gly Met Lys Phe Met Ala Ala Val Ala Phe Leu Ala Leu Gln Leu
5 10 15
Ile Val Met Ala Ala Ala Glu Asp Gln Ser Ala Gln Ile Met Leu Asp
20 25 30
Ser Asp Ile Glu Gln Tyr Leu Arg Ser Asn Arg Ser Leu Lys Lys Leu
35 40 45
Val His Ser Arg His Asp Ala Ala Thr Val Phe Asn Val Glu Gln Tyr
50 55 60
Gly Ala Val Gly Asp Gly Lys His Asp Ser Thr Glu Ala Phe Ala Thr
65 70 75 80
Thr Trp Asn Ala Ala Cys Lys Lys Ala Ser Ala Val Leu Leu Val Pro
85 90 95

Ala Asn Lys Lys Phe Phe Val Asn Asn Leu Val Phe Arg Gly Pro Cys
100 105 110
Gln Pro His Leu Ser Phe Lys Val Asp Gly Thr Ile Val Ala Gln Pro
115 120 125
Asp Pro Ala Arg Trp Lys Asn Ser Lys Ile Trp Leu Gln Phe Ala Gln
130 135 140
Leu Thr Asp Phe Asn Leu Met Gly Thr Gly Val Ile Asp Gly Gln Gly
145 150 155 160
Gln Gln Trp Trp Ala Gly Gln Cys Lys Val Val Asn Gly Arg Thr Val
165 170 175
Cys Asn Asp Arg Asn Arg Pro Thr Ala Ile Lys Ile Asp Tyr Ser Lys
180 185 190
Ser Val Thr Val Lys Glu Leu Thr Leu Met Asn Ser Pro Glu Phe His
195 200 205
Leu Val Phe Gly Glu Cys Glu Gly Val Lys Ile Gln Gly Leu Lys Ile
210 215 220
Lys Ala Pro Arg Asp Ser Pro Asn Thr Asp Gly Ile Asp Ile Phe Ala
225 230 235 240
Ser Lys Arg Phe His Ile Glu Lys Cys Val Ile Gly Thr Gly Asp Asp
245 250 255
Cys Ile Ala Ile Gly Thr Gly Ser Ser Asn Ile Thr Ile Lys Asp Leu
260 265 270
Ile Cys Gly Pro Gly His Gly Ile Ser Ile Gly Ser Leu Gly Arg Asp
275 280 285
Asn Ser Arg Ala Glu Val Ser His Val His Val Asn Arg Ala Lys Phe
290 295 300
Ile Asp Thr Gln Asn Gly Leu Arg Ile Lys Thr Trp Gln Gly Gly Ser
305 310 315 320
Gly Leu Ala Ser Tyr Ile Thr Tyr Glu Asn Val Glu Met Ile Asn Ser
325 330 335
Glu Asn Pro Ile Leu Ile Asn Gln Phe Tyr Cys Thr Ser Ala Ser Ala
340 345 350
Cys Gln Asn Gln Arg Ser Ala Val Gln Ile Gln Gly Val Thr Tyr Lys
355 360 365
Asn Ile His Gly Thr Ser Ala Thr Ala Ala Ala Ile Gln Leu Met Cys
370 375 380

Ser Asp Ser Val Pro Cys Thr Gly Ile Gln Leu Ser Asn Val Ser Leu
385 390 395 400
Lys Leu Thr Ser Gly Lys Pro Ala Ser Cys Val Asp Lys Asn Ala Arg
405 410 415
Gly Phe Tyr Ser Gly Arg Leu Ile Pro Thr Cys Lys Asn Leu Arg Pro
420 425 430
Gly Pro Ser Pro Lys Glu Phe Glu Leu Gln Gln Gln Pro Thr Thr Val
435 440 445
Met Asp Glu Asn Lys Gly Ala Cys Ala Lys Gly Asp Ser Thr Cys Ile
450 455 460
Ser Leu Ser Ser Ser Pro Pro Asn Cys Lys Asn Lys Cys Lys Gly Cys
465 470 475 480
Gln Pro Cys Lys Pro Lys Leu Ile Ile Val His Pro Asn Lys Pro Gln
485 490 495
Asp Tyr Tyr Pro Gln Lys Trp Val Cys Ser Cys His Asn Lys Ile Tyr
500 505 510
Asn Pro

SEQ ID NO: 3:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:
Asp Asn Pro Ile Asp Ser Cys Trp Arg Gly Asp Ala Asn Trp Asp Gln
1 5 10 15
Asn Arg Met Lys
20

SEQ ID NO: 4:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:
Asp Ala Asn Trp Asp Gln Asn Arg Met Lys Leu Ala Asp Cys Ala Val

1 5 10 15

Gly Phe Gly Ser
20

SEQ ID NO: 5:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

Leu Ala Asp Cys Ala Val Gly Phe Gly Ser Ser Ala Met Gly Gly Lys
1 5 10 15

Gly Gly Ala Phe
20

SEQ ID NO: 6:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

Ser Ala Met Gly Gly Lys Gly Gly Ala Phe Tyr Thr Val Thr Ser Ser
1 5 10 15

Asp Asp Asp Pro
20

SEQ ID NO: 7:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

Tyr Thr Val Thr Ser Ser Asp Asp Asp Pro Val Asn Pro Ala Pro Gly
1 5 10 15

Thr Leu Arg Tyr
20

SEQ ID NO: 8:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

```
Val Asn Pro Ala Pro Gly Thr Leu Arg Tyr Gly Ala Thr Arg Glu Arg
 1               5                  10                  15
Ser Leu Trp Ile
            20
```

SEQ ID NO: 9:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

```
Gly Ala Thr Arg Glu Arg Ser Leu Trp Ile Ile Phe Ser Lys Asn Leu
 1               5                  10                  15
Asn Ile Lys Leu
            20
```

SEQ ID NO: 10:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

```
Ile Phe Ser Lys Asn Leu Asn Ile Lys Leu Asn Met Pro Leu Tyr Ile
 1               5                  10                  15
Ala Gly Asn Lys
            20
```

SEQ ID NO: 11:
SEQUENCE LENGTH: 20

SEQUENCE TYPE: amino acid

TOPOLOGY: linear

MOLECULE TYPE: peptide

SEQUENCE DESCRIPTION:

Asn Met Pro Leu Tyr Ile Ala Gly Asn Lys Thr Ile Asp Gly Arg Gly

1 5 10 15

Ala Glu Val His

20

SEQ ID NO: 12:

SEQUENCE LENGTH: 20

SEQUENCE TYPE: amino acid

TOPOLOGY: linear

MOLECULE TYPE: peptide

SEQUENCE DESCRIPTION:

Thr Ile Asp Gly Arg Gly Ala Glu Val His Ile Gly Asn Gly Gly Pro

1 5 10 15

Cys Leu Phe Met

20

SEQ ID NO: 13:

SEQUENCE LENGTH: 20

SEQUENCE TYPE: amino acid

TOPOLOGY: linear

MOLECULE TYPE: peptide

SEQUENCE DESCRIPTION:

Ile Gly Asn Gly Gly Pro Cys Leu Phe Met Arg Thr Val Ser His Val

1 5 10 15

Ile Leu His Gly

20

SEQ ID NO: 14:

SEQUENCE LENGTH: 20

SEQUENCE TYPE: amino acid

TOPOLOGY: linear

MOLECULE TYPE: peptide

SEQUENCE DESCRIPTION:

Arg Thr Val Ser His Val Ile Leu His Gly Leu Asn Ile His Gly Cys
1 5 10 15

Asn Thr Ser Val
20

SEQ ID NO: 15:

SEQUENCE LENGTH: 20

SEQUENCE TYPE: amino acid

TOPOLOGY: linear

MOLECULE TYPE: peptide

SEQUENCE DESCRIPTION:

Leu Asn Ile His Gly Cys Asn Thr Ser Val Ser Gly Asn Val Leu Ile
1 5 10 15

Ser Glu Ala Ser
20

SEQ ID NO: 16:

SEQUENCE LENGTH: 20

SEQUENCE TYPE: amino acid

TOPOLOGY: linear

MOLECULE TYPE: peptide

SEQUENCE DESCRIPTION:

Ser Gly Asn Val Leu Ile Ser Glu Ala Ser Gly Val Val Pro Val His
1 5 10 15

Ala Gln Asp Gly
20

SEQ ID NO: 17:

SEQUENCE LENGTH: 20

SEQUENCE TYPE: amino acid

TOPOLOGY: linear

MOLECULE TYPE: peptide

SEQUENCE DESCRIPTION:

Gly Val Val Pro Val His Ala Gln Asp Gly Asp Ala Ile Thr Met Arg
1 5 10 15

Asn Val Thr Asp
20

SEQ ID NO: 18:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:
Asp Ala Ile Thr Met Arg Asn Val Thr Asp Val Trp Ile Asp His Asn
1 5 10 15
Ser Leu Ser Asp
20

SEQ ID NO: 19:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:
Val Trp Ile Asp His Asn Ser Leu Ser Asp Ser Ser Asp Gly Leu Val
1 5 10 15
Asp Val Thr Leu
20

SEQ ID NO: 20:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:
Ser Ser Asp Gly Leu Val Asp Val Thr Leu Ala Ser Thr Gly Val Thr
1 5 10 15
Ile Ser Asn Asn
20

SEQ ID NO: 21:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

```
Ala Ser Thr Gly Val Thr Ile Ser Asn Asn His Phe Phe Asn His His
 1               5                  10                  15
Lys Val Met Leu
            20
```

SEQ ID NO: 22:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

```
His Phe Phe Asn His His Lys Val Met Leu Leu Gly His Ser Asp Ile
 1               5                  10                  15
Tyr Ser Asp Asp
            20
```

SEQ ID NO: 23:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

```
Leu Gly His Ser Asp Ile Tyr Ser Asp Asp Lys Ser Met Lys Val Thr
 1               5                  10                  15
Val Ala Phe Asn
            20
```

SEQ ID NO: 24:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid

TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

```
Lys Ser Met Lys Val Thr Val Ala Phe Asn Gln Phe Gly Pro Asn Ala
 1               5                  10                  15
Gly Gln Arg Met
            20
```

SEQ ID NO: 25:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

```
Gln Phe Gly Pro Asn Ala Gly Gln Arg Met Pro Arg Ala Arg Tyr Gly
 1               5                  10                  15
Leu Ile His Val
            20
```

SEQ ID NO: 26:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

```
Pro Arg Ala Arg Tyr Gly Leu Ile His Val Ala Asn Asn Asn Tyr Asp
 1               5                  10                  15
Pro Trp Ser Ile
            20
```

SEQ ID NO: 27:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

Ala Asn Asn Asn Tyr Asp Pro Trp Ser Ile Tyr Ala Ile Gly Gly Ser
1 5 10 15
Ser Asn Pro Thr
20

SEQ ID NO: 28:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:
Tyr Ala Ile Gly Gly Ser Ser Asn Pro Thr Ile Leu Ser Glu Gly Asn
1 5 10 15
Ser Phe Thr Ala
20

SEQ ID NO: 29:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:
Ile Leu Ser Glu Gly Asn Ser Phe Thr Ala Pro Asn Asp Ser Asp Lys
1 5 10 15
Lys Glu Val Thr
20

SEQ ID NO: 30:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:
Pro Asn Asp Ser Asp Lys Lys Glu Val Thr Arg Arg Val Gly Cys Glu
1 5 10 15
Ser Pro Ser Thr

20

SEQ ID NO: 31:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

Arg Arg Val Gly Cys Glu Ser Pro Ser Thr Cys Ala Asn Trp Val Trp
1 5 10 15

Arg Ser Thr Gln
20

SEQ ID NO: 32:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

Cys Ala Asn Trp Val Trp Arg Ser Thr Gln Asp Ser Phe Asn Asn Gly
1 5 10 15

Ala Tyr Phe Val
20

SEQ ID NO: 33:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

Asp Ser Phe Asn Asn Gly Ala Tyr Phe Val Ser Ser Gly Lys Asn Glu
1 5 10 15

Gly Thr Asn Ile
20

SEQ ID NO: 34:

SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

Ser Ser Gly Lys Asn Glu Gly Thr Asn Ile Tyr Asn Asn Asn Glu Ala
1 5 10 15

Phe Lys Val Glu
20

SEQ ID NO: 35:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

Tyr Asn Asn Asn Glu Ala Phe Lys Val Glu Asn Gly Ser Ala Ala Pro
1 5 10 15

Gln Leu Thr Lys
20

SEQ ID NO: 36:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

Asn Gly Ser Ala Ala Pro Gln Leu Thr Lys Asn Ala Gly Val Leu Thr
1 5 10 15

Cys Ile Leu Ser
20

SEQ ID NO: 37:
SEQUENCE LENGTH: 14
SEQUENCE TYPE: amino acid
TOPOLOGY: linear

MOLECULE TYPE: peptide

SEQUENCE DESCRIPTION:

Asn Ala Gly Val Leu Thr Cys Ile Leu Ser Lys Pro Cys Ser

1 5 10

SEQ ID NO: 38:

SEQUENCE LENGTH: 20

SEQUENCE TYPE: amino acid

TOPOLOGY: linear

MOLECULE TYPE: peptide

SEQUENCE DESCRIPTION:

Met Gly Met Lys Phe Met Ala Ala Val Ala Phe Leu Ala Leu Gln Leu

1 5 10 15

Ile Val Met Ala

20

SEQ ID NO: 39:

SEQUENCE LENGTH: 20

SEQUENCE TYPE: amino acid

TOPOLOGY: linear

MOLECULE TYPE: peptide

SEQUENCE DESCRIPTION:

Phe Leu Ala Leu Gln Leu Ile Val Met Ala Ala Ala Glu Asp Gln Ser

1 5 10 15

Ala Gln Ile Met

20

SEQ ID NO: 40:

SEQUENCE LENGTH: 20

SEQUENCE TYPE: amino acid

TOPOLOGY: linear

MOLECULE TYPE: peptide

SEQUENCE DESCRIPTION:

Ala Ala Glu Asp Gln Ser Ala Gln Ile Met Leu Asp Ser Asp Ile Glu

1 5 10 15

Gln Tyr Leu Arg

20

SEQ ID NO: 41:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

Leu Asp Ser Asp Ile Glu Gln Tyr Leu Arg Ser Asn Arg Ser Leu Lys
1 5 10 15
Lys Leu Val His
20

SEQ ID NO: 42:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

Ser Asn Arg Ser Leu Lys Lys Leu Val His Ser Arg His Asp Ala Ala
1 5 10 15
Thr Val Phe Asn
20

SEQ ID NO: 43:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

Ser Arg His Asp Ala Ala Thr Val Phe Asn Val Glu Gln Tyr Gly Ala
1 5 10 15
Val Gly Asp Gly
20

SEQ ID NO: 44:

SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

```
Val Glu Gln Tyr Gly Ala Val Gly Asp Gly Lys His Asp Ser Thr Glu
 1               5                  10                  15
Ala Phe Ala Thr
            20
```

SEQ ID NO: 45:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

```
Lys His Asp Ser Thr Glu Ala Phe Ala Thr Thr Trp Asn Ala Ala Cys
 1               5                  10                  15
Lys Lys Ala Ser
            20
```

SEQ ID NO: 46:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

```
Thr Trp Asn Ala Ala Cys Lys Lys Ala Ser Ala Val Leu Leu Val Pro
 1               5                  10                  15
Ala Asn Lys Lys
            20
```

SEQ ID NO: 47:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear

MOLECULE TYPE: peptide

SEQUENCE DESCRIPTION:

Ala Val Leu Leu Val Pro Ala Asn Lys Lys Phe Phe Val Asn Asn Leu
1 5 10 15

Val Phe Arg Gly
20

SEQ ID NO: 48:

SEQUENCE LENGTH: 20

SEQUENCE TYPE: amino acid

TOPOLOGY: linear

MOLECULE TYPE: peptide

SEQUENCE DESCRIPTION:

Phe Phe Val Asn Asn Leu Val Phe Arg Gly Pro Cys Gln Pro His Leu
1 5 10 15

Ser Phe Lys Val
20

SEQ ID NO: 49:

SEQUENCE LENGTH: 20

SEQUENCE TYPE: amino acid

TOPOLOGY: linear

MOLECULE TYPE: peptide

SEQUENCE DESCRIPTION:

Pro Cys Gln Pro His Leu Ser Phe Lys Val Asp Gly Thr Ile Val Ala
1 5 10 15

Gln Pro Asp Pro
20

SEQ ID NO: 50:

SEQUENCE LENGTH: 20

SEQUENCE TYPE: amino acid

TOPOLOGY: linear

MOLECULE TYPE: peptide

SEQUENCE DESCRIPTION:

Asp Gly Thr Ile Val Ala Gln Pro Asp Pro Ala Arg Trp Lys Asn Ser

1 5 10 15

Lys Ile Trp Leu

20

SEQ ID NO: 51:

SEQUENCE LENGTH: 20

SEQUENCE TYPE: amino acid

TOPOLOGY: linear

MOLECULE TYPE: peptide

SEQUENCE DESCRIPTION:

Ala Arg Trp Lys Asn Ser Lys Ile Trp Leu Gln Phe Ala Gln Leu Thr

1 5 10 15

Asp Phe Asn Leu

20

SEQ ID NO: 52

SEQUENCE LENGTH: 20

SEQUENCE TYPE: amino acid

TOPOLOGY: linear

MOLECULE TYPE: peptide

SEQUENCE DESCRIPTION:

Gln Phe Ala Gln Leu Thr Asp Phe Asn Leu Met Gly Thr Gly Val Ile

1 5 10 15

Asp Gly Gln Gly

20

SEQ ID NO: 53:

SEQUENCE LENGTH: 20

SEQUENCE TYPE: amino acid

TOPOLOGY: linear

MOLECULE TYPE: peptide

SEQUENCE DESCRIPTION:

Met Gly Thr Gly Val Ile Asp Gly Gln Gly Gln Gln Trp Trp Ala Gly

1 5 10 15

Gln Cys Lys Val

20

SEQ ID NO: 54:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

```
Gln Gln Trp Trp Ala Gly Gln Cys Lys Val Val Asn Gly Arg Thr Val
 1               5                  10                  15
Cys Asn Asp Arg
            20
```

SEQ ID NO: 55:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

```
Val Asn Gly Arg Thr Val Cys Asn Asp Arg Asn Arg Pro Thr Ala Ile
 1               5                  10                  15
Lys Ile Asp Tyr
            20
```

SEQ ID NO: 56:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

```
Asn Arg Pro Thr Ala Ile Lys Ile Asp Tyr Ser Lys Ser Val Thr Val
 1               5                  10                  15
Lys Glu Leu Thr
            20
```

SEQ ID NO: 57:
SEQUENCE LENGTH: 20

SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

```
Ser Lys Ser Val Thr Val Lys Glu Leu Thr Leu Met Asn Ser Pro Glu
 1               5                  10                  15
Phe His Leu Val
            20
```

SEQ ID NO: 58:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

```
Leu Met Asn Ser Pro Glu Phe His Leu Val Phe Gly Glu Cys Glu Gly
 1               5                  10                  15
Val Lys Ile Gln
            20
```

SEQ ID NO: 59:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

```
Phe Gly Glu Cys Glu Gly Val Lys Ile Gln Gly Leu Lys Ile Lys Ala
 1               5                  10                  15
Pro Arg Asp Ser
            20
```

SEQ ID NO: 60:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide

SEQUENCE DESCRIPTION:

Gly Leu Lys Ile Lys Ala Pro Arg Asp Ser Pro Asn Thr Asp Gly Ile
1 5 10 15

Asp Ile Phe Ala
20

SEQ ID NO: 61:

SEQUENCE LENGTH: 20

SEQUENCE TYPE: amino acid

TOPOLOGY: linear

MOLECULE TYPE: peptide

SEQUENCE DESCRIPTION:

Pro Asn Thr Asp Gly Ile Asp Ile Phe Ala Ser Lys Arg Phe His Ile
1 5 10 15

Glu Lys Cys Val
20

SEQ ID NO: 62:

SEQUENCE LENGTH: 20

SEQUENCE TYPE: amino acid

TOPOLOGY: linear

MOLECULE TYPE: peptide

SEQUENCE DESCRIPTION:

Ser Lys Arg Phe His Ile Glu Lys Cys Val Ile Gly Thr Gly Asp Asp
1 5 10 15

Cys Ile Ala Ile
20

SEQ ID NO: 63:

SEQUENCE LENGTH: 20

SEQUENCE TYPE: amino acid

TOPOLOGY: linear

MOLECULE TYPE: peptide

SEQUENCE DESCRIPTION:

Ile Gly Thr Gly Asp Asp Cys Ile Ala Ile Gly Thr Gly Ser Ser Asn
1 5 10 15

Ile Thr Ile Lys
20

SEQ ID NO: 64:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:
Gly Thr Gly Ser Ser Asn Ile Thr Ile Lys Asp Leu Ile Cys Gly Pro
1 5 10 15
Gly His Gly Ile
20

SEQ ID NO: 65:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:
Asp Leu Ile Cys Gly Pro Gly His Gly Ile Ser Ile Gly Ser Leu Gly
1 5 10 15
Arg Asp Asn Ser
20

SEQ ID NO: 66:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:
Ser Ile Gly Ser Leu Gly Arg Asp Asn Ser Arg Ala Glu Val Ser His
1 5 10 15
Val His Val Asn
20

SEQ ID NO: 67:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

Arg Ala Glu Val Ser His Val His Val Asn Arg Ala Lys Phe Ile Asp
1 5 10 15

Thr Gln Asn Gly
20

SEQ ID NO: 68:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

Arg Ala Lys Phe Ile Asp Thr Gln Asn Gly Leu Arg Ile Lys Thr Trp
1 5 10 15

Gln Gly Gly Ser
20

SEQ ID NO: 69:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

Leu Arg Ile Lys Thr Trp Gln Gly Gly Ser Gly Leu Ala Ser Tyr Ile
1 5 10 15

Thr Tyr Glu Asn
20

SEQ ID NO: 70:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid

TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

```
Gly Leu Ala Ser Tyr Ile Thr Tyr Glu Asn Val Glu Met Ile Asn Ser
 1               5                  10                  15
Glu Asn Pro Ile
            20
```

SEQ ID NO: 71:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

```
Val Glu Met Ile Asn Ser Glu Asn Pro Ile Leu Ile Asn Gln Phe Tyr
 1               5                  10                  15
Cys Thr Ser Ala
            20
```

SEQ ID NO: 72:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

```
Leu Ile Asn Gln Phe Tyr Cys Thr Ser Ala Ser Ala Cys Gln Asn Gln
 1               5                  10                  15
Arg Ser Ala Val
            20
```

SEQ ID NO: 73:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

Ser Ala Cys Gln Asn Gln Arg Ser Ala Val Gln Ile Gln Gly Val Thr
1 5 10 15
Tyr Lys Asn Ile
20

SEQ ID NO: 74:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:
Gln Ile Gln Gly Val Thr Tyr Lys Asn Ile His Gly Thr Ser Ala Thr
1 5 10 15
Ala Ala Ala Ile
20

SEQ ID NO: 75:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:
His Gly Thr Ser Ala Thr Ala Ala Ala Ile Gln Leu Met Cys Ser Asp
1 5 10 15
Ser Val Pro Cys
20

SEQ ID NO: 76:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:
Gln Leu Met Cys Ser Asp Ser Val Pro Cys Thr Gly Ile Gln Leu Ser
1 5 10 15
Asn Val Ser Leu

20

SEQ ID NO: 77:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

Thr Gly Ile Gln Leu Ser Asn Val Ser Leu Lys Leu Thr Ser Gly Lys
1 5 10 15

Pro Ala Ser Cys
20

SEQ ID NO: 78:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

Lys Leu Thr Ser Gly Lys Pro Ala Ser Cys Val Asp Lys Asn Ala Arg
1 5 10 15

Gly Phe Tyr Ser
20

SEQ ID NO: 79:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

Val Asp Lys Asn Ala Arg Gly Phe Tyr Ser Gly Arg Leu Ile Pro Thr
1 5 10 15

Cys Lys Asn Leu
20

SEQ ID NO: 80:

SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

```
Gly Arg Leu Ile Pro Thr Cys Lys Asn Leu Arg Pro Gly Pro Ser Pro
 1               5                  10                  15
Lys Glu Phe Glu
            20
```

SEQ ID NO: 81:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

```
Arg Pro Gly Pro Ser Pro Lys Glu Phe Glu Leu Gln Gln Gln Pro Thr
 1               5                  10                  15
Thr Val Met Asp
            20
```

SEQ ID NO: 82:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

```
Leu Gln Gln Gln Pro Thr Thr Val Met Asp Glu Asn Lys Gly Ala Cys
 1               5                  10                  15
Ala Lys Gly Asp
            20
```

SEQ ID NO: 83:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear

MOLECULE TYPE: peptide

SEQUENCE DESCRIPTION:

Glu Asn Lys Gly Ala Cys Ala Lys Gly Asp Ser Thr Cys Ile Ser Leu
1 5 10 15

Ser Ser Ser Pro
20

SEQ ID NO: 84:

SEQUENCE LENGTH: 20

SEQUENCE TYPE: amino acid

TOPOLOGY: linear

MOLECULE TYPE: peptide

SEQUENCE DESCRIPTION:

Ser Thr Cys Ile Ser Leu Ser Ser Ser Pro Pro Asn Cys Lys Asn Lys
1 5 10 15

Cys Lys Gly Cys
20

SEQ ID NO: 85:

SEQUENCE LENGTH: 20

SEQUENCE TYPE: amino acid

TOPOLOGY: linear

MOLECULE TYPE: peptide

SEQUENCE DESCRIPTION:

Pro Asn Cys Lys Asn Lys Cys Lys Gly Cys Gln Pro Cys Lys Pro Lys
1 5 10 15

Leu Ile Ile Val
20

SEQ ID NO: 86:

SEQUENCE LENGTH: 20

SEQUENCE TYPE: amino acid

TOPOLOGY: linear

MOLECULE TYPE: peptide

SEQUENCE DESCRIPTION:

Gln Pro Cys Lys Pro Lys Leu Ile Ile Val His Pro Asn Lys Pro Gln

1 5 10 15

Asp Tyr Tyr Pro
20

SEQ ID NO: 87:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

His Pro Asn Lys Pro Gln Asp Tyr Tyr Pro Gln Lys Trp Val Cys Ser
1 5 10 15

Cys His Asn Lys
20

SEQ ID NO: 88:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

Gln Lys Trp Val Cys Ser Cys His Asn Lys Ile Tyr Asn Pro
1 5 10

SEQ ID NO: 89:
SEQUENCE LENGTH: 20
SEQUENCE TYPE: amino acid
TOPOLOGY: linear
MOLECULE TYPE: peptide
SEQUENCE DESCRIPTION:

Phe Phe Val Asn Asn Leu Val Phe Arg Gly Pro Cys Gln Pro His Leu
1 5 10 15

Pro Phe Lys Val
20

SEQ ID NO: 90:

SEQUENCE LENGTH: 20

SEQUENCE TYPE: amino acid

TOPOLOGY: linear

MOLECULE TYPE: peptide

SEQUENCE DESCRIPTION:

```
Pro Cys Gln Pro His Leu Pro Phe Lys Val Asp Gly Thr Ile Val Ala
 1               5                  10                  15
Gln Pro Asp Pro
            20
```

Claims

1. A peptide comprising at least one T-cell epitope of Japanese cypress pollen allergen Cha o 1 and having an amino acid sequence selected from Peptide #1-2 (SEQ ID NO: 4), Peptide #1-4 (SEQ ID NO: 6), Peptide #1-5 (SEQ ID NO: 7), Peptide #1-6 (SEQ ID NO: 8), Peptide #1-7 (SEQ ID NO: 9), Peptide #1-8 (SEQ ID NO: 10), Peptide #1-10 (SEQ ID NO: 12), Peptide #1-11 (SEQ ID NO: 13), Peptide #1-12 (SEQ ID NO: 14), Peptide #1-14 (SEQ ID NO: 16), Peptide #1-15 (SEQ ID NO: 17), Peptide #1-16 (SEQ ID NO: 18), Peptide #1-19 (SEQ ID NO: 21), Peptide #1-20 (SEQ ID NO: 22), Peptide #1-21 (SEQ ID NO: 23), Peptide #1-22 (SEQ ID NO: 24), Peptide #1-23 (SEQ ID NO: 25), Peptide #1-24 (SEQ ID NO: 26), Peptide #1-25 (SEQ ID NO: 27), Peptide #1-26 (SEQ ID NO: 28), Peptide #1-27 (SEQ ID NO: 29), Peptide #1-30 (SEQ ID NO: 32), Peptide #1-31 (SEQ ID NO: 33), Peptide #1-32 (SEQ ID NO: 34), Peptide #1-33 (SEQ ID NO: 35), and Peptide #1-34 (SEQ ID NO: 36) shown in Fig. 4, or a part of said amino acid sequence.

2. A peptide comprising at least one T-cell epitope of Japanese cypress pollen allergen Cha o 2 and having an amino acid sequence selected from Peptide #2-5 (SEQ ID NO: 42), Peptide #2-7 (SEQ ID NO: 44), Peptide #2-8 (SEQ ID NO: 45), Peptide #2-9 (SEQ ID NO: 46), Peptide #2-10 (SEQ ID NO: 47), Peptide #2-11 (SEQ ID NO: 48), Peptide #2-12 (SEQ ID NO: 49), Peptide #2-13 (SEQ ID NO: 50), Peptide #2-14 (SEQ ID NO: 51), Peptide #2-15 (SEQ ID NO: 52), Peptide #2-16 (SEQ ID NO: 53), Peptide #2-17 (SEQ ID NO: 54), Peptide #2-18 (SEQ ID NO: 55),

Peptide #2-19 (SEQ ID NO: 56), Peptide #2-20 (SEQ ID NO: 57), Peptide #2-21 (SEQ ID NO: 58), Peptide #2-22 (SEQ ID NO: 59), Peptide #2-23 (SEQ ID NO: 60), Peptide #2-24 (SEQ ID NO: 61), Peptide #2-25 (SEQ ID NO: 62), Peptide #2-26 (SEQ ID NO: 63), Peptide #2-27 (SEQ ID NO: 64), Peptide #2-30 (SEQ ID NO: 67), Peptide #2-31 (SEQ ID NO: 68), Peptide #2-32 (SEQ ID NO: 69), Peptide #2-33 (SEQ ID NO: 70) and Peptide #2-34 (SEQ ID NO: 71), Peptide #2-35 (SEQ ID NO: 72), Peptide #2-36 (SEQ ID NO: 73), Peptide #2-37 (SEQ ID NO: 74), Peptide #2-38 (SEQ ID NO: 75), Peptide #2-40 (SEQ ID NO: 77), Peptide #2-41 (SEQ ID NO: 78), Peptide #2-42 (SEQ ID NO: 79), and Peptide #2-43 (SEQ ID NO: 80) shown in Fig. 8, or a part of said amino acid sequence.

3. The peptide of claim 1 or 2, wherein said peptide comprises at least two T-cell epitopes.

4. A peptide having an effect to stimulate and/or suppress activities of T-cells derived from patients with pollinosis caused by tree pollens in springtime and having the amino acid sequence as described in claim 1 or 2 which is modified by substitution, deletion, or insertion.

5. A composition for peptide-based immunotherapy of pollinosis caused by tree pollens in springtime, comprising the peptide of any one of claims 1 to 4 as an effective ingredient.

6. Use of the peptide of any one of claims 1 to 4 for preparing a composition for peptide-based immunotherapy of pollinosis caused by tree pollens in springtime.

7. A method for treating or preventing pollinosis caused

by tree pollens in springtime, comprising administering the peptide of any one of claims 1 to 4.

8. A reagent for diagnosing pollinosis caused by tree pollens in springtime, comprising the peptide of any one of claims 1 to 4 as an effective ingredient.

9. Use of the peptide of any one of claims 1 to 4 for preparing a reagent for diagnosing pollinosis caused by tree pollens in springtime.

10. A method for diagnosing pollinosis caused by tree pollens in springtime, comprising administering the peptide of any one of claims 1 to 4.

Abstract

The T-cell epitope site on a Japanese cypress (*hinoki*) pollen allergen molecule has been identified by stimulating a T-cell line established from a patient suffering from Japanese cypress pollen allergy with an overlap peptide covering the primary structure of the Japanese cypress pollen allergen. The peptide is useful in peptide-based immunotherapy for patients with spring tree pollinosis including patients with Japanese cypress pollinosis having cross reactivity with Japanese cypress pollen. The peptide is also useful for diagnosing spring tree pollinosis.

Fig. 1

Peptide No.	mean stimulation index	appearance frequency (%)
rCha o 1	7.0	100
(1)		0
(2)	2.0	32
(3)		0
(4)	1.0	5
(5)	1.4	11
(6)	1.4	16
(7)	3.2	68
(8)	2.4	37
(9)		0
(10)	1.5	26
(11)	1.7	21
(12)	1.5	16
(13)		0
(14)	1.1	5
(15)	1.1	5
(16)	1.6	11
(17)		0
(18)		0
(19)	1.4	16
(20)	2.1	37
(21)	1.8	26
(22)	5.1	74
(23)	1.1	5
(24)	2.1	32
(25)	1.7	16
(26)	2.1	42
(27)	1.1	5
(28)		0
(29)		0
(30)	1.1	11
(31)	1.5	11
(32)	2.8	47
(33)	2.8	53
(34)	2.0	26
(35)		0

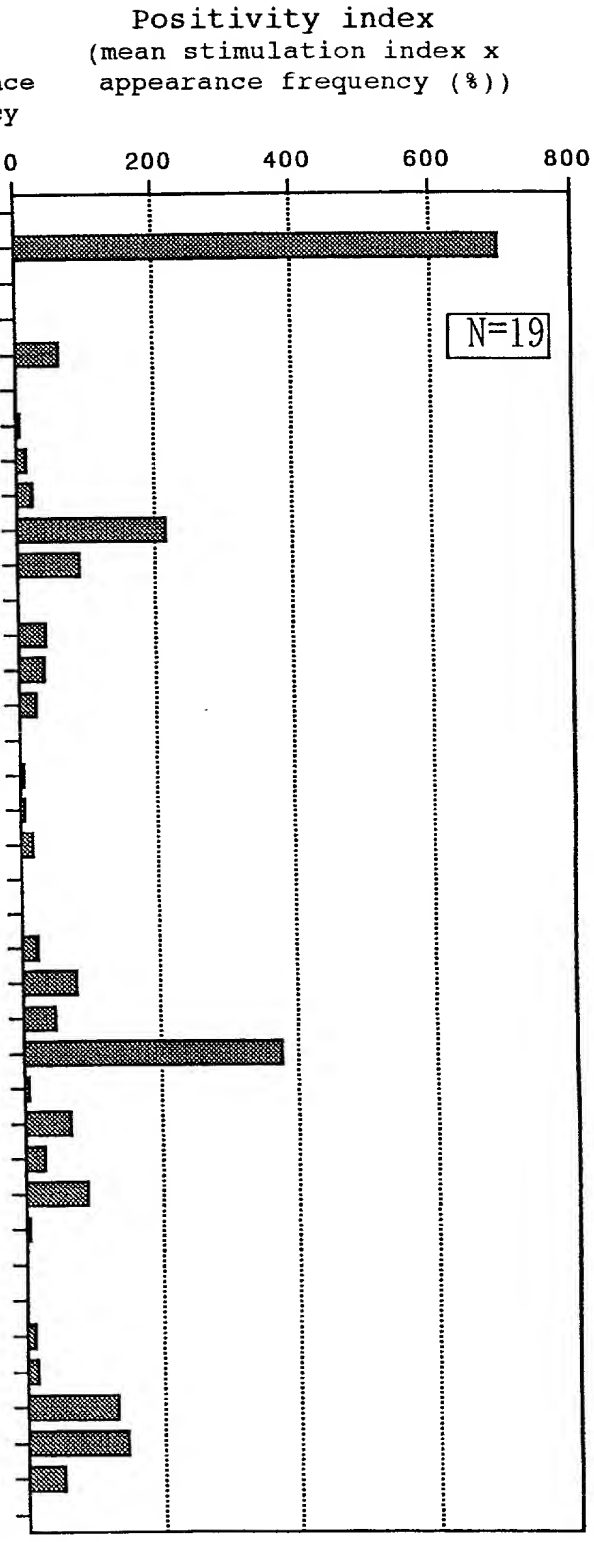

Fig. 2

#1-1(1-20). D N P I D S C W R G D A N W D Q N R M K

#1-2(11-30). D A N W D Q N R M K L A D C A V G F G S

#1-3(21-40). L A D C A V G F G S S A M G G K G G A F

#1-4(31-50). S A M G G K G G A F Y T V T S S D D D P

#1-5(41-60). Y T V T S S D D D P V N P A P G T L R Y

#1-6(51-70). V N P A P G T L R Y G A T R E R S L W I

#1-7(61-80). G A T R E R S L W I I F S K N L N I K L

#1-8(71-90). I F S K N L N I K L N M P L Y I A G N K

#1-9(81-100). N M P L Y I A G N K T I D G R G A E V H

#1-10(91-110). T I D G R G A E V H I G N G G P C L F M

#1-11(101-120). I G N G G P C L F M R T V S H V I L H G

#1-12(111-130). R T V S H V I L H G L N I H G C N T S V

#1-13(121-140). L N I H G C N T S V S G N V L I S E A S

#1-14(131-150). S G N V L I S E A S G V V P V H A Q D G

#1-15(141-160). G V V P V H A Q D G D A I T M R N V T D

#1-16(151-170). D A I T M R N V T D V W I D H N S L S D

#1-17(161-180). V W I D H N S L S D S S D G L V D V T L

#1-18(171-190). S S D G L V D V T L A S T G V T I S N N

#1-19(181-200). A S T G V T I S N N H F F N H H K V M L

#1-20(191-210). H F F N H H K V M L L G H S D I Y S D D

#1-21(201-220). L G H S D I Y S D D K S M K V T V A F N

#1-22(211-230). K S M K V T V A F N Q F G P N A G Q R M

#1-23(221-240). Q F G P N A G Q R M P R A R Y G L I H V

#1-24(231-250). P R A R Y G L I H V A N N N Y D P W S I

#1-25(241-260). A N N N Y D P W S I Y A I G G S S N P T

#1-26(251-270). Y A I G G S S N P T I L S E G N S F T A

#1-27(261-280). I L S E G N S F T A P N D S D K K E V T

#1-28(271-290). P N D S D K K E V T R R V G C E S P S T

Fig. 3

#1-29(281-300). R R V G C E S P S T C A N W V W R S T Q

#1-30(291-310). C A N W V W R S T Q D S F N N G A Y F V

#1-31(301-320). D S F N N G A Y F V S S G K N E G T N I

#1-32(311-330). S S G K N E G T N I Y N N N E A F K V E

#1-33(321-340). Y N N N E A F K V E N G S A A P Q L T K

#1-34(331-350). N G S A A P Q L T K N A G V L T C I L S

#1-35(341-354). N A G V L T C I L S K P C S

Fig. 4

#1-2(11-30). D A N W D Q N R M K L A D C A V G F G S

#1-4(31-50). S A M G G K G G A F Y T V T S S D D D P

#1-5(41-60). Y T V T S S D D D P V N P A P G T L R Y

#1-6(51-70). V N P A P G T L R Y G A T R E R S L W I

#1-7(61-80). G A T R E R S L W I I F S K N L N I K L

#1-8(71-90). I F S K N L N I K L N M P L Y I A G N K

#1-10(91-110). T I D G R G A E V H I G N G G P C L F M

#1-11(101-120). I G N G G P C L F M R T V S H V I L H G

#1-12(111-130). R T V S H V I L H G L N I H G C N T S V

#1-14(131-150). S G N V L I S E A S G V V P V H A Q D G

#1-15(141-160). G V V P V H A Q D G D A I T M R N V T D

#1-16(151-170). D A I T M R N V T D V W I D H N S L S D

#1-19(181-200). A S T G V T I S N N H F F N H H K V M L

#1-20(191-210). H F F N H H K V M L L G H S D I Y S D D

#1-21(201-220). L G H S D I Y S D D K S M K V T V A F N

#1-22(211-230). K S M K V T V A F N Q F G P N A G Q R M

#1-23(221-240). Q F G P N A G Q R M P R A R Y G L I H V

#1-24(231-250). P R A R Y G L I H V A N N N Y D P W S I

#1-25(241-260). A N N N Y D P W S I Y A I G G S S N P T

#1-26(251-270). Y A I G G S S N P T I L S E G N S F T A

#1-27(261-280). I L S E G N S F T A P N D S D K K E V T

#1-30(291-310). C A N W V W R S T Q D S F N N G A Y F V

#1-31(301-320). D S F N N G A Y F V S S G K N E G T N I

#1-32(311-330). S S G K N E G T N I Y N N N E A F K V E

#1-33(321-340). Y N N N E A F K V E N G S A A P Q L T K

#1-34(331-350). N G S A A P Q L T K N A G V L T C I L S

Fig. 5

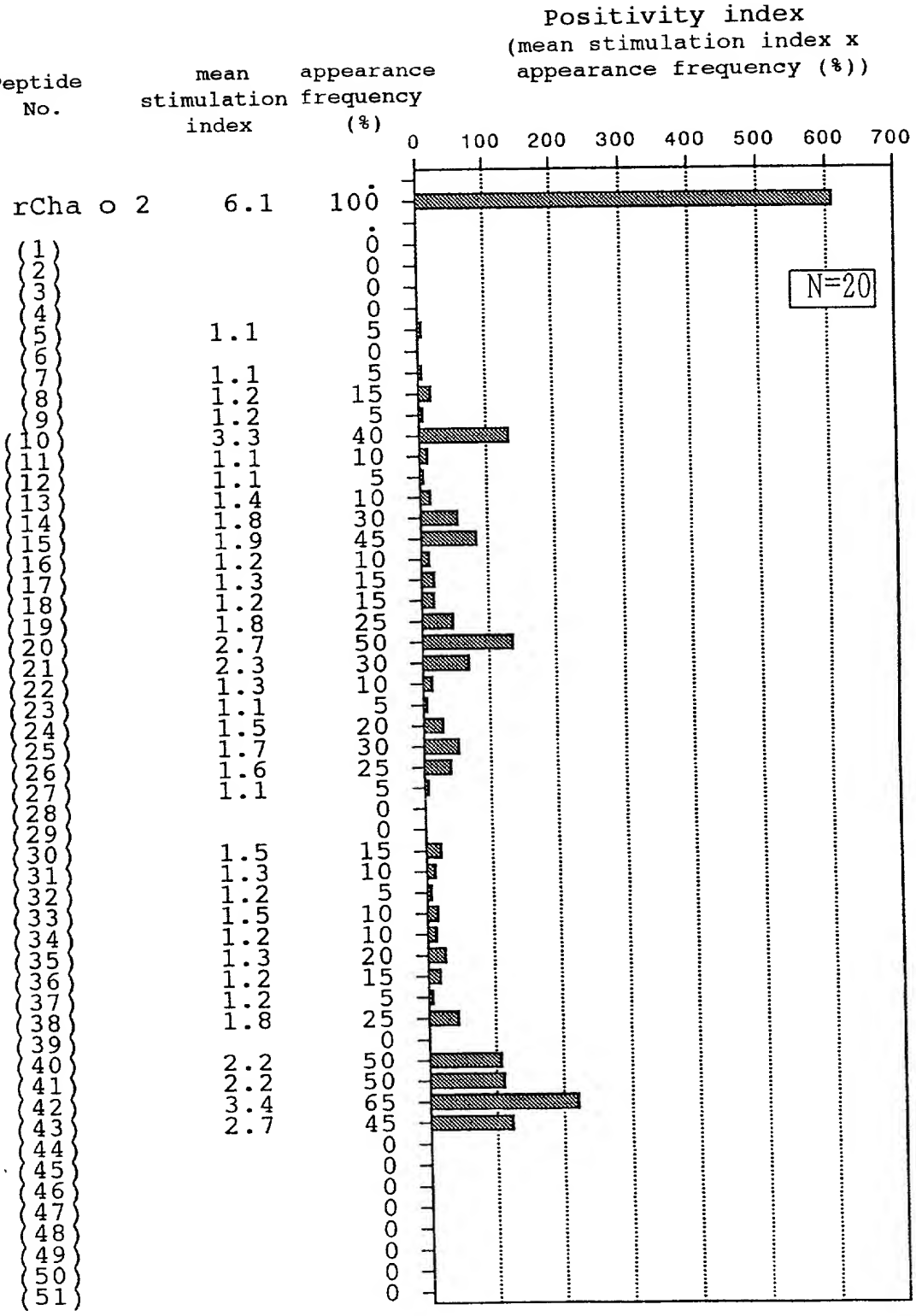
Positivity index
(mean stimulation index x appearance frequency (%))
Peptide No.
mean stimulation index
appearance frequency (%)
0
100
200
300
400
500
600
700
N=20
rCha o 2 6.1 100
(1) 0
2 0
3 0
4 0
5 1.1 5
6 0
7 1.1 5
8 1.2 15
9 1.2 5
(10) 3.3 40
(11) 1.1 10
12 1.1 5
13 1.4 10
14 1.8 30
15 1.9 45
16 1.2 10
17 1.3 15
18 1.2 15
19 1.8 25
20 2.7 50
21 2.3 30
22 1.3 10
23 1.1 5
24 1.5 20
25 1.7 30
26 1.6 25
27 1.1 5
28 0
29 0
30 1.5 15
31 1.3 10
32 1.2 5
33 1.5 10
34 1.2 10
35 1.3 20
36 1.2 15
37 1.2 5
38 1.8 25
39 0
40 2.2 50
41 2.2 50
42 3.4 65
43 2.7 45
44 0
45 0
46 0
47 0
48 0
49 0
50 0
(51) 0

Fig. 6

#2-1(1-20).	M G M K F M A A V A F L A L Q L I V M A
#2-2(11-30).	F L A L Q L I V M A A A E D Q S A Q I M
#2-3(21-40).	A A E D Q S A Q I M L D S D I E Q Y L R
#2-4(31-50).	L D S D I E Q Y L R S N R S L K K L V H
#2-5(41-60).	S N R S L K K L V H S R H D A A T V F N
#2-6(51-70).	S R H D A A T V F N V E Q Y G A V G D G
#2-7(61-80).	V E Q Y G A V G D G K H D S T E A F A T
#2-8(71-90).	K H D S T E A F A T T W N A A C K K A S
#2-9(81-100).	T W N A A C K K A S A V L L V P A N K K
#2-10(91-110).	A V L L V P A N K K F F V N N L V F R G
#2-11(101-120).	F F V N N L V F R G P C Q P H L S F K V
#2-12(111-130).	P C Q P H L S F K V D G T I V A Q P D P
#2-13(121-140).	D G T I V A Q P D P A R W K N S K I W L
#2-14(131-150).	A R W K N S K I W L Q F A Q L T D F N L
#2-15(141-160).	Q F A Q L T D F N L M G T G V I D G Q G
#2-16(151-170).	M G T G V I D G Q G Q Q W W A G Q C K V
#2-17(161-180).	Q Q W W A G Q C K V V N G R T V C N D R
#2-18(171-190).	V N G R T V C N D R N R P T A I K I D Y
#2-19(181-200).	N R P T A I K I D Y S K S V T V K E L T
#2-20(191-210).	S K S V T V K E L T L M N S P E F H L V
#2-21(201-220).	L M N S P E F H L V F G E C E G V K I Q
#2-22(211-230).	F G E C E G V K I Q G L K I K A P R D S
#2-23(221-240).	G L K I K A P R D S P N T D G I D I F A
#2-24(231-250).	P N T D G I D I F A S K R F H I E K C V
#2-25(241-260).	S K R F H I E K C V I G T G D D C I A I
#2-26(251-270).	I G T G D D C I A I G T G S S N I T I K
#2-27(261-280).	G T G S S N I T I K D L I C G P G H G I

Fig. 7

#2-28(271-290). D L I C G P G H G I S I G S L G R D N S
#2-29(281-300). S I G S L G R D N S R A E V S H V H V N
#2-30(291-310). R A E V S H V H V N R A K F I D T Q N G
#2-31(301-320). R A K F I D T Q N G L R I K T W Q G G S
#2-32(311-330). L R I K T W Q G G S G L A S Y I T Y E N
#2-33(321-340). G L A S Y I T Y E N V E M I N S E N P I
#2-34(331-350). V E M I N S E N P I L I N Q F Y C T S A
#2-35(341-360). L I N Q F Y C T S A S A C Q N Q R S A V
#2-36(351-370). S A C Q N Q R S A V Q I Q G V T Y K N I
#2-37(361-380). Q I Q G V T Y K N I H G T S A T A A A I
#2-38(371-390). H G T S A T A A A I Q L M C S D S V P C
#2-39(381-400). Q L M C S D S V P C T G I Q L S N V S L
#2-40(391-410). T G I Q L S N V S L K L T S G K P A S C
#2-41(401-420). K L T S G K P A S C V D K N A R G F Y S
#2-42(411-430). V D K N A R G F Y S G R L I P T C K N L
#2-43(421-440). G R L I P T C K N L R P G P S P K E F E
#2-44(431-450). R P G P S P K E F E L Q Q Q P T T V M D
#2-45(441-460). L Q Q Q P T T V M D E N K G A C A K G D
#2-46(451-470). E N K G A C A K G D S T C I S L S S S P
#2-47(461-480). S T C I S L S S S P P N C K N K C K G C
#2-48(471-490). P N C K N K C K G C Q P C K P K L I I V
#2-49(481-500). Q P C K P K L I I V H P N K P Q D Y Y P
#2-50(491-510). H P N K P Q D Y Y P Q K W V C S C H N K
#2-51(501-514). Q K W V C S C H N K I Y N P

Fig. 8

#2-5(41-60). S N R S L K K L V H S R H D A A T V F N
#2-7(61-80). V E Q Y G A V G D G K H D S T E A F A T
#2-8(71-90). K H D S T E A F A T T W N A A C K K A S
#2-9(81-100). T W N A A C K K A S A V L L V P A N K K
#2-10(91-110). A V L L V P A N K K F F V N N L V F R G
#2-11(101-120). F F V N N L V F R G P C Q P H L S F K V
#2-12(111-130). P C Q P H L S F K V D G T I V A Q P D P
#2-13(121-140). D G T I V A Q P D P A R W K N S K I W L
#2-14(131-150). A R W K N S K I W L Q F A Q L T D F N L
#2-15(141-160). Q F A Q L T D F N L M G T G V I D G Q G
#2-16(151-170). M G T G V I D G Q G Q Q W W A G Q C K V
#2-17(161-180). Q Q W W A G Q C K V V N G R T V C N D R
#2-18(171-190). V N G R T V C N D R N R P T A I K I D Y
#2-19(181-200). N R P T A I K I D Y S K S V T V K E L T
#2-20(191-210). S K S V T V K E L T L M N S P E F H L V
#2-21(201-220). L M N S P E F H L V F G E C E G V K I Q
#2-22(211-230). F G E C E G V K I Q G L K I K A P R D S
#2-23(221-240). G L K I K A P R D S P N T D G I D I F A
#2-24(231-250). P N T D G I D I F A S K R F H I E K C V
#2-25(241-260). S K R F H I E K C V I G T G D D C I A I
#2-26(251-270). I G T G D D C I A I G T G S S N I T I K
#2-27(261-280). G T G S S N I T I K D L I C G P G H G I
#2-30(291-310). R A E V S H V H V N R A K F I D T Q N G
#2-31(301-320). R A K F I D T Q N G L R I K T W Q G G S
#2-32(311-330). L R I K T W Q G G S G L A S Y I T Y E N
#2-33(321-340). G L A S Y I T Y E N V E M I N S E N P I
#2-34(331-350). V E M I N S E N P I L I N Q F Y C T S A
#2-35(341-360). L I N Q F Y C T S A S A C Q N Q R S A V
#2-36(351-370). S A C Q N Q R S A V Q I Q G V T Y K N I
#2-37(361-380). Q I Q G V T Y K N I H G T S A T A A A I
#2-38(371-390). H G T S A T A A A I Q L M C S D S V P C
#2-40(391-410). T G I Q L S N V S L K L T S G K P A S C
#2-41(401-420). K L T S G K P A S C V D K N A R G F Y S
#2-42(411-430). V D K N A R G F Y S G R L I P T C K N L
#2-43(421-440). G R L I P T C K N L R P G P S P K E F E

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COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled T-CELL EPITOPE PEPTIDES, the specification of which

☐ is attached hereto.
☐ was filed on _____ as Application Serial No. _____ and was amended on _____.
■ was described and claimed in PCT International Application No. PCT/JP97/02031 filed on 12 JUNE 1997 and was amended on _____.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose all information I know to be material to patentability in accordance with Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

COUNTRY	APPLICATION NO.	FILING DATE	PRIORITY CLAIMED
JP	8/153527	14 JUNE 1996	■ Yes ☐ No

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose all information I know to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56(a) which became available between the filing date of the prior application and the national or PCT international filing date of this application:

U.S. SERIAL NO.	FILING DATE	STATUS
PCT/JP97/02031	12 JUNE 1997	■ Pending ☐ Issued ☐ Abandoned

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

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